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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,953	01/23/2004	Xianqi Kong	NBI-193	5062

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LAHIVE & COCKFIELD, LLP
ONE POST OFFICE SQUARE
BOSTON, MA 02109-2127

EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	PAPER NUMBER
1626	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/26/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,953	KONG ET AL.	
	Examiner	Art Unit	
	Jason M. Nolan, Ph.D.	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,23,25 and 26* is/are pending in the application.

4a) Of the above claim(s) *1-7* is/are withdrawn from consideration.

5)☒ Claim(s) *8 and 23* is/are allowed.

6)☒ Claim(s) *25 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8, 23, 25 & 26 are currently pending in the instant application; of which **Claims 1-7** are withdrawn and **Claim 23** is amended. **Claims 9-22 & 24** are cancelled.

Response to Amendment

The Declaration filed on 10/27/2006 under 37 CFR 1.131 is sufficient to overcome the Chalifour *et al.* reference.

The objections to **Claims 8, 25 & 26** are withdrawn per amendment to **Claim 23**.

Allowable Subject Matter

Claims 8 & 23 are allowed. The elected group from the Restriction Requirement dated 10/14/2005 has been fully examined. **Claims 1-7** remain withdrawn as drawn to a non-elected invention; the restriction between Groups I and II is final.

Claim Rejections - 35 USC § 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25 & 26 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for compositions of the amidine derivatives shown in **Claim 8**, does not reasonably provide enablement for the treatment or prevention of an

amyloid-related disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in the MPEP 2164.01(a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'."

In re Wands, 8 USPQ2d 1400 (1988), discusses the following factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph:

1. ***The nature of the invention;***
2. ***The state of the prior art;***
3. ***The predictability or lack thereof in the art;***
4. ***The amount of direction or guidance present;***
5. ***The presence or absence of working examples;***
6. ***The breadth of the claims;***
7. ***The quantity of experimentation needed; and***
8. ***The level of skill in the art.***

The nature of the invention

Drug design is the approach of finding drugs by design, based on their biological targets. Typically a drug target is a key molecule involved in a particular metabolic or signalling pathway that is specific to a disease condition or pathology, or to the infectivity or survival of a microbial pathogen. Some approaches attempt to stop the functioning of the pathway in the diseased state by causing a key molecule to stop functioning. Drugs may be designed that bind to the active region and inhibit this key

molecule. However these drugs would also have to be designed in such a way as not to affect any other important molecules that may be similar in appearance to the key molecules. Other approaches may be to enhance the normal pathway by promoting specific molecules in the normal pathways that may have been affected in the diseased state. The structure of the drug molecule that can specifically interact with the biomolecules can be modeled using computational tools. These tools can allow a drug molecule to be constructed within the biomolecule using knowledge of its structure and the nature of its active site. Construction of the drug molecule can be made inside out or outside in depending on whether the core or the R-groups are chosen first.

In the instant application, the nature of the invention is compounds and compositions (the amidine derivatives shown in **Claim 8**) for the treatment of an amyloid-related disease. The relevant biological mechanisms are discussed on page 4, lines 1-7.

The state of the prior, and the predictability or lack thereof in the art

Highly sophisticated tools for rational drug design still have not taken the unpredictability out of this complex art; it still requires trial and error experimentation. The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary

skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In the instant case, the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compositions may provide a treatment for one or some amyloid-related diseases, but it does not mean that the same group of compositions may prevent any amyloid-related diseases or treat all amyloid-related diseases. Since these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face, a substantial amount of biological data and correlative information is required to enable the skilled artisan to use the invention as claimed.

The amount of direction or guidance present, and the presence or absence of working examples

The amidine compounds (and compositions) disclosed in the instant application, in one embodiment "prevent or inhibit amyloid protein assembly into soluble fibrils which, *in vivo*, are deposited in various organs...", (page 4, lines 1-3). However, stated on page 2, lines 10-13 of the instant specification, "Once these amyloids have formed, there is no known, widely accepted therapy or treatment which significantly dissolves

amyloid depostis in situ or that prevents further amyloid deposition. There is also no widely known or accepted therapy or treatment which prevents amyloid deposition from occurring." With this in mind, the specification would be expected to provide working examples establishing the claim that the compounds and compositions clamed therein are able to treat amyloid-related diseases via the biological pathways outlined on page 4, lines 1-3. However, no working examples are present.

The breadth of the claims

Claim 25 encompasses an immense number of species, reciting "an amyloid-related disease". **Claim 26** limits the genus to Alzheimer's disease, Down's syndrome, type II diabetes, Mild Cognitive Impairment, age-related macular degeneration, or cerebral amyloid angiopathy. Although limiting the genus to six species (diseases), the diseases of **Claim 26** are drastically different such that no known pharmaceutical treats said diseases.

The quantity of experimentation needed, and the level of skill in the art

Claims 25 & 26 are drawn to "a pharmaceutical composition for the treatment or prevention of an amyloid-related disease." In order to prevent a disease, one would need to precisely identify those subjects likely to acquire such a disease, administer Applicant's claimed invention, and then demonstrate that if the identified subject did not develop the disease, such an effect was the direct result of administration of the claimed invention. In order to treat a disease, one would need to identify which species (composition) claimed herein has the desired effect as outlined for the biological

pathways outlined on page 4, lines 1-3, and further identify which species (specific disease) said composition is useful for treating via said pathway.

Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success. This rejection may be overcome by canceling **Claims 25 & 26**.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is **Jason.Nolan@uspto.gov**. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jason M. Nolan, Ph.D.
Examiner
Art Unit 1626

KAMAL A. SAEED, PH.D.
PRIMARY EXAMINER

Joseph K. M^{c}Kane
Supervisory Patent Examiner
Art Unit 1626
Date: December 19, 2006